

## REMARKS

As a preliminary matter, applicants acknowledge with appreciation the Examiner's holding the Office Action under reply as non-final; however, applicants take issue with the Examiner's statement that the newly cited art, i.e., Honeyman et al. and Hogan et al., were not discovered until after the BAPI Decision on Appeal. Hogan et al., which is cited in the Background of the instant application, was the first cited reference in the Information Disclosure Statement (IDS) filed with the application papers on September 15, 2003 (reference AA). Honeyman et al. was submitted in the IDS filed on August 2, 2004 (reference BI). Both Honeyman et al. and Hogan et al. were acknowledged by the Examiner as considered in the attachments to the Office Action of August 9, 2006.

## REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-5, 9-14, 26, and 32 stand rejected under 35 U.S.C. § 102(b) as anticipated by Honeyman et al. This rejection is traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992).

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

As recited in claim 32, the present invention is directed to a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the

secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

Honeyman et al. teach a snapback method of single-stranded conformation polymorphism (SSCP) analysis for genotyping Golden Retrievers for the X-linked muscular dystrophy allele (Abstract). At column 1 of page 734, Honeyman et al. explain that the causative mutation of the X-linked form of muscular dystrophy in Golden Retrievers is a single base change within the 3' splice site of intron 6 in the canine dystrophin gene. The mutation results in a loss of exon 7 and disruption of the reading frame so that transcription of the dystrophin gene is prematurely truncated by an in-frame stop codon in exon 8.

As explained by Honeyman et al. at column 2 of page 734, the truncation of the dystrophin gene results in difficulties in genotyping the dogs. While two PCR procedures can be used to overcome the genotyping difficulties, Honeyman et al. acknowledge that using two PCR procedures is time consuming and cumbersome. As an alternative to the two PCR approach, Honeyman et al. suggest the use of SSCP analyses. Honeyman et al. explain that SSCP analysis is a quick, simple method of detecting genetic mutations. The method involves diluting and heat denaturing PCR products in formamide loading buffer and fractionating the material on a polyacrylamide gel under nondenaturing conditions. No manipulations of the PCR product besides gel fractionation are required. Honeyman et al. note that one limitation of SSCP analysis is that many base changes, up to 30%, may be missed. Honeyman et al. provide that the missed base changes typically occur in regions that are not involved in the overall secondary or tertiary structure of the single-stranded PCR products, such as for example, the X-linked muscular dystrophy gene mutation seen in Golden Retrievers (*see also*, the Discussion at page 736, column 1).

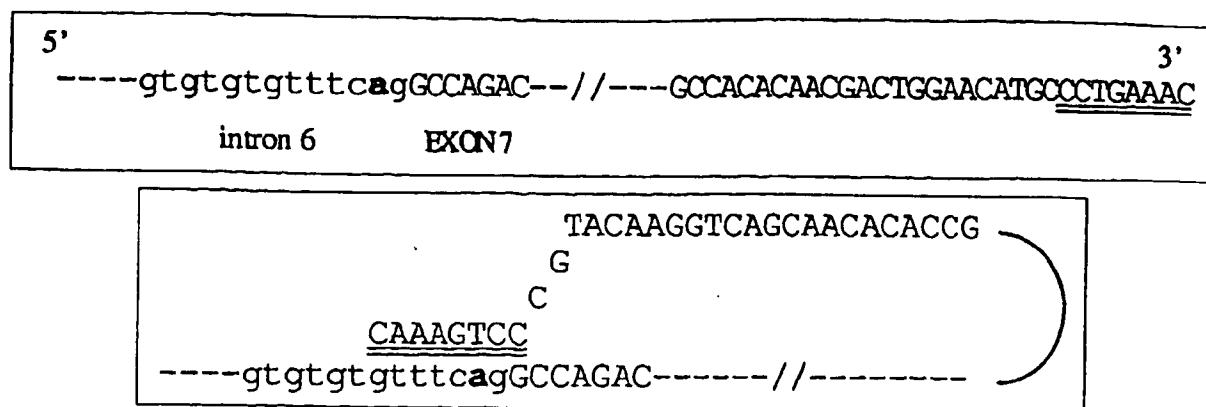
To overcome the limitation in the SSCP analysis, Honeyman et al. developed a snapback method of SSCP analysis where a snapback primer is designed using one of the original primers to which an additional sequence that is complementary to the normal sequence flanking the mutation under investigation is added to the 5' terminus. The snapback primer replaces the original forward or reverse primer used in the PCR procedure, with the result that PCR products

of the snapback primer will have a terminus with the potential of reannealing or snapping back to the normal allele, but not to the mutant allele. With the Honeyman et al. snapback primer, a region containing the mutation under investigation is forced into playing a role in the secondary and tertiary structures of the single-stranded PCR products. In other words, as a result of the snapback, the PCR products of the normal dogs will have secondary or tertiary structure conformation changes, while the PCR products of the mutant dogs will not. As explained in column one of page 736 and as shown in Figure 2, as a result of the conformational secondary or tertiary structure change in the snapback SSCP PCR product, the snapback SSCP PCR product migrates at a different rate than the conventional SSCP PCR product. As shown in Figure 2, the PCR product for the unaffected (N), carrier (C), and affected dogs (A) migrated at different rates with the snapback SSCP primers, but not with the conventional SSCP primers (*see also*, para. bridging pp. 735-736 and page 736, col. 1, 1<sup>st</sup> full para.). As noted on page 736 (col. 1, 1<sup>st</sup> full para., last line), the nucleotide mismatch in the mutant allele prevented the snapback, which resulted in a faster migration of the PCR product on the fractionated gel (Figure 2).

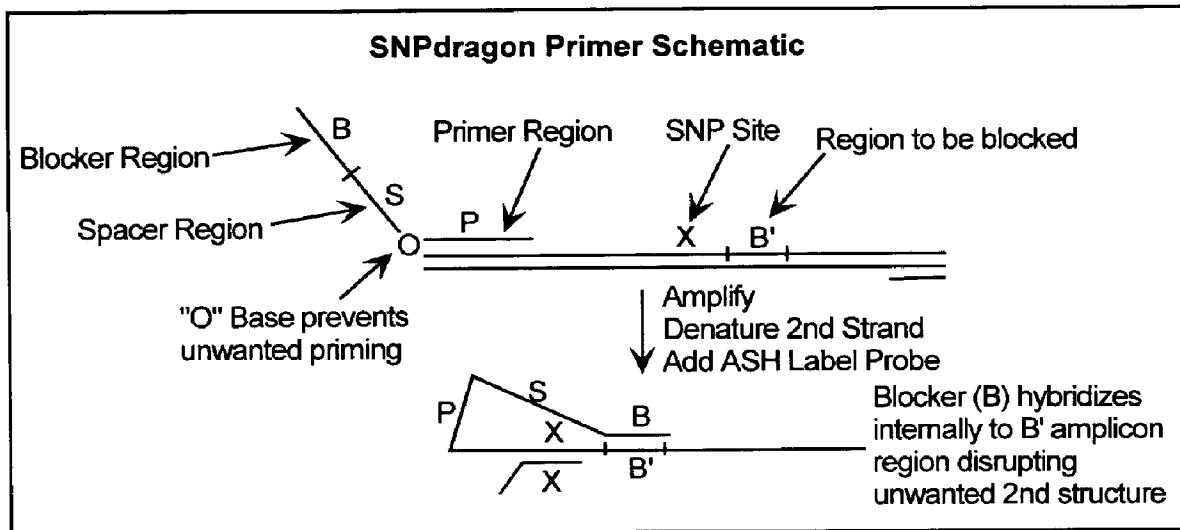
At page 736, column 2, Honeyman et al. teach that the use of a primer at as great a distance as possible from the normal sequence flanking the mutation site was optimal because the arrangement generated the most substantial single-strand conformation change. Honeyman et al. explain that snapback primers that were designed to anneal only a few bases away from the normal sequence flanking the mutation were successful for detecting the mutant allele, but not the normal product. Honeyman et al. attribute this behavior to the 3' end of the normal reverse strand snapping back on itself forming a hairpin structure and reducing amplification efficiency of the normal product. By contrast, snapback primers designed to anneal at least 70 bases from the normal sequence flanking the mutation did not engage in self-priming.

The method of Honeyman et al. is illustrated in Figure 3, which shows the nucleotide sequences involved in the snapback genotyping analysis of Golden Retriever puppies from a colony of dogs with X-linked muscular dystrophy. The top portion of Figure 3 shows a portion of the sequence for the normal allele of the canine dystrophin gene. In dogs with muscular dystrophy, an adenine residue (shown in bold in the figure) in the 3' splice site of intron 6 is replaced by a guanosine residue (shown in lower case letters). Also shown in Figure 3 is the priming site for the GR1-SB snapback primer (the last 8 nucleotides shown in underlined upper case letters). The bottom portion of Figure 3 shows the last 8 nucleotides snapping back and

priming to the 3' end of the forward single strand of the amplified normal allele. Figure 3 clearly shows that the snapback process of Honeyman et al. involves a single stranded DNA with a snapback primer annealed some distance from the site of interest (i.e., the SNP at intron 6 in exon 7) snapping back and priming to the site of interest to form a loop (i.e., a secondary structure) wherein the site of interest is primed to the last 8 nucleotides of the single-stranded DNA. Applicants have provided a reproduction of Figure 3 of Honeyman et al. for the Examiner's convenience.



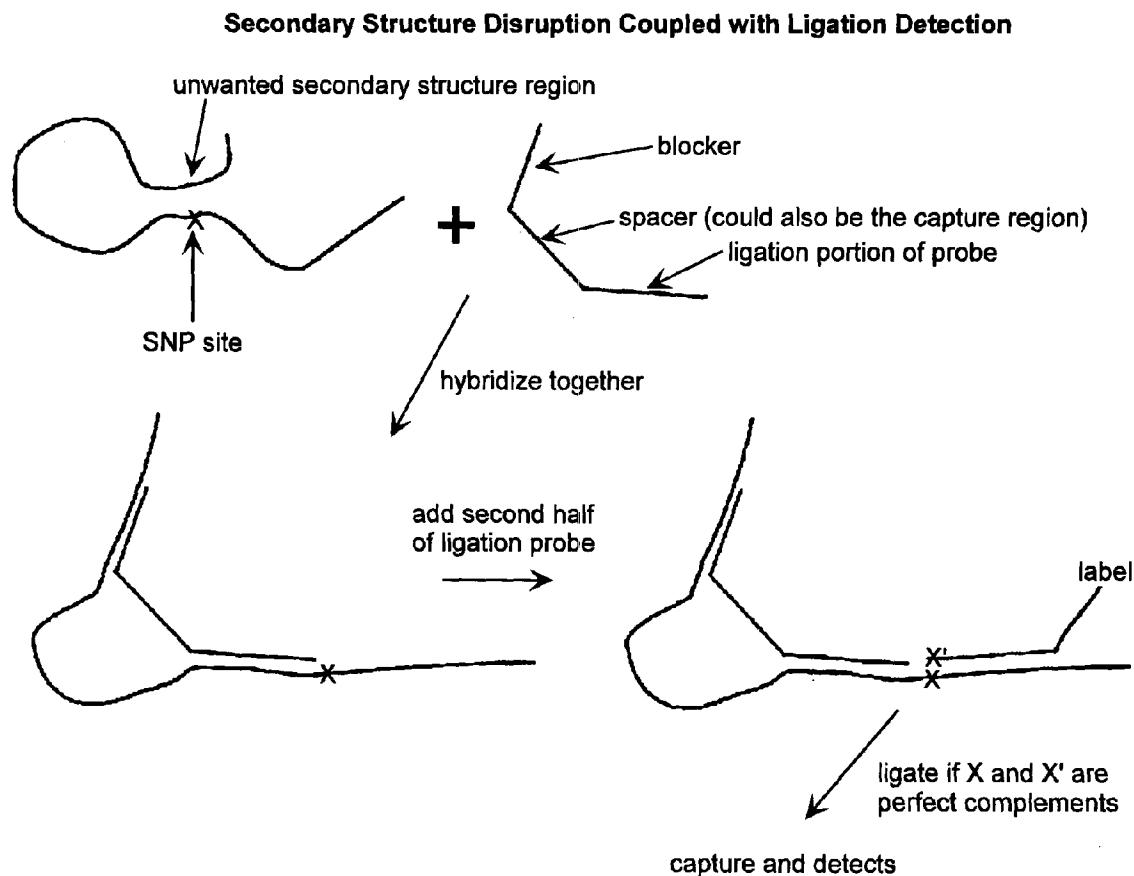
As applicants have explained in prior Office Action responses and as is clear from a proper reading of the claims of the instant application, the claimed invention is not directed to a procedure by which an SNP site becomes part of the secondary structure formed in a single-stranded nucleic acid sequence, rather, the claimed primers and probes *disrupt* secondary structures that conceal an SNP. Figures 5 and 10 of the instant application illustrate how the primer of the claimed invention works. For the Examiner's convenience, applicants are reproducing Figures 5 and 10 so that the Examiner may compare the difference between Figure 3 of Honeyman et al., which illustrates the procedure of Honeyman et al. and Figures 5 and 10 of the instant application, which illustrates the primers and probes of the claimed invention.



**FIG. 5**

As explained in paragraphs 0019 and 0057 of the specification of the instant application, Figure 5 schematically illustrates the structure and mechanism of action of the dual-purpose primer of the claimed invention. The primer sequence is complementary to one terminus of the target molecule that contains the SNP site (X) and the blocking sequence is substantially complementary to a sequence B' immediately adjacent to X, wherein B' is the segment of the target molecule responsible for generating an intramolecular secondary structure that, in the absence of the claimed dual purpose primer, would conceal the SNP site from a complementary sequence (thereby preventing hybridization and detection). After amplification of the target nucleotide sequence and reannealing, B hybridizes with B' in the amplicon, blocking formation of the unwanted secondary structure and allowing the SNP site to be detected and amplified.

The foregoing explanation of Figure 5 shows schematically how different the claimed invention is from Honeyman et al. In Honeyman et al., the SNP site is within the linear single stranded DNA and the 3' terminal 8 nucleotides of the GR1-SB snapback primer *snap back and hybridize to the site with the SNP*. By contrast, with the claimed invention, the SNP site is hidden within a secondary structure and *the blocking sequence binds to the secondary structure thus exposing the SNP site*. Figure 10 further illustrates this feature of the claimed invention.

**FIG. 10**

Turning to the substance of the Examiner's rejection, at pages 3 of the Office Action, the Examiner takes the position that the claimed primers and probes are the same as the "Honeyman" primer set forth on page 4 of the Office Action. Applicants note that the "Honeyman" primer on page 4 of the Office Action is the same as the GF2 primer sequence set forth on page 735 of Honeyman et al.

On page 735 of Honeyman et al., it is taught that for *conventional* SSCP analysis, primers GF2 (forward primer) and GR1 (reverse primer) were used. Honeyman et al. teach that the GF2 primer corresponds to basepairs 135 through 114 of the canine dystrophin gene (intron 6) and that the GR1 primer corresponds to basepairs 805 through 782 (exon 7). The GF2 and GR1 primers of Honeyman et al. have the following sequences.

GF2 (intron 6): 5'-CTT AAG GAA TGA TGG GCA TGG G-3'

GR1 (exon 7): 5'-TGC ATG TTC CAG TCG TTG TGT GGC-3'

For the snapback SSCP analysis, primer GR1 and a snapback primer GR1-SB were used. Honeyman et al. teach that the GR1-SB snapback primer was designed by replacing the 5' terminal thymine of the GR1 primer (highlighted in the GR1 primer above with underlining) with a GTTTCAGG sequence (highlighted in the GR1-SB primer below with underlining). The GR1-SB snapback primer has the following sequence.

GR1-SB: 5'-GTTTCAGGGC ATG TTC CAG TCG TTG TGT GGC-3'

Figure 3 shows how the complement to the GR1-SB snapback primer on exon 7 (3'-CAAAGTCC) hybridizes to the complementary target sequence on intron 6 (5'-*gtttcagg*) thus forming the snapback loop, which has already been discussed in detail above.

As noted above, the Examiner's "Honeyman" primer sequence on page 4 of the Office Action is the GF2 primer sequence. The Examiner asserts that Honeyman et al. teach that this sequence includes the priming sequence (a) and the blocking sequence (b) of the claimed invention. The Examiner highlights the portion of the GF2 sequence that she believes reads on the primer sequence (a) of the claimed invention with underlining and the portion that she believes reads on the blocking sequence (b) of the claimed invention with italics. The sequence as highlighted by the Examiner on page 4 of the Office Action is reproduced below:

5'-CTT AAG GAA TGA TGG GCA TGG G-3'

As discussed above, Honeyman et al. used the GF2 and the GR1 primers for conventional SSCP analysis and the GR1-SB primer for the snapback analysis. On page 3 of the Office Action, the Examiner correctly identifies the site of interest of the canine dystrophin gene disclosed in Honeyman et al. as the adenine-guanosine replacement site on intron 6 identified in bold in the sequence GTTTCAG; this sequence is identical to the 5' terminal sequence added to the GR1 primer to form the GR1-SB primer. Despite these teachings, the Honeyman et al. site of interest does not appear in the Examiner's "Target" sequence set forth on page 4 of the Office Action and the complement (CAAAGTC) does not appear anywhere in the GF2 primer. Furthermore, a review of Honeyman et al. shows that contrary to the Examiner's position, Honeyman et al. do not teach or suggest that the sequence underlined by the Examiner (AAGGAAT) is complementary to a segment of the target nucleic acid other than a secondary structure forming region or that the italicized sequence (GATCC) is blocking secondary structure formation. In the Office Action under reply, the Examiner attempts to correct these omissions in the teachings of Honeyman et al. by stating that the teachings are inherent. Applicants disagree.

Honeyman et al. do not inherently teach that the sequence AAGGAAT is complementary to a segment of the target nucleic acid other than a secondary structure forming region or that the sequence GATCC is blocking secondary structure formation. The most that Honeyman et al. inherently teaches is that the GF2 primer may have the following single-stranded complementary sequence.

GF2 (intron 6): 5'-CTT AAG GAA TGA TGG GCA TGG G-3'

Complement: 3'-GAA TTC CTT ACT ACC CGT ACC C-5'

Further, with respect to secondary structure formation, as noted above, Honeyman et al. expressly teach that the mutations that could not be detected using the conventional SSCP primers (such as the forward GF2 primer used by the Examiner) are those mutations that are *not* involved in the secondary or tertiary structure of the single stranded PCR product (p.734, col. 2; p.736, col. 1). These express teachings combined with the additional express teaching from Honeyman et al. that the GF2 primer was not able to distinguish mutant from normal or carrier dogs (para. bridging pp. 735-736, col. 1; Fig. 2) leads to the inherent teaching that the GF2 primer is priming to a site on the X-linked muscular dystrophin gene that has no secondary or tertiary structure. Indeed, this deficiency in the target gene is the precise reason that Honeyman et al. developed the snapback SSCP primer; specifically, to introduce single stranded conformational changes to the PCR product (Fig. 3) so that the migration of the mutant PCR product would be different from the migration of the normal and carrier PCR products (Fig. 2).

If the Examiner's inherency reasoning comes from a source other than Honeyman et al., then pursuant to MPEP §2144.03, applicants request that the Examiner provide the source to applicants. If the Examiner's inherency reasoning is based upon judicial notice of facts not in the record or of information that the Examiner considers to be common knowledge in the art, then pursuant to MPEP § 2144.03, applicants request that the Examiner provide documentary evidence to support the judicial notice or the information that the Examiner considers to be common knowledge in the art. If the Examiner's inherency reasoning stems from personal knowledge, then pursuant to MPEP § 2144.03 and 37 C.F.R. 1.104(d)(2), applicants request that the Examiner submit an Affidavit or Declaration that introduces the Examiner's personal knowledge into the record for this case, along with a detailed description of how the Examiner's personal knowledge would lead the Examiner to interpret Honeyman et al. as set forth in the Office Action under reply.

Because the snapback and conventional SSCP primers of Honeyman et al. do not expressly or inherently anticipate the claimed primers and probes for the reasons set forth above, applicants request withdrawal of this rejection.

**REJECTION UNDER 35 U.S.C. § 103(a) – Honeyman et al. and Laibinis**

Claims 6-8, 15, and 16 stand rejected under 35 U.S.C. § 103(a) as obvious over Honeyman et al. in view of Laibinis et al. This rejection is traversed.

The Examiner cites Laibinis et al. for the non-hybridizing spacer and arresting linker of claim 6-8, 15, and 16. Claims 6-8, 15, and 16 depend from claim 1. Because Honeyman et al. do not teach or suggest claim 1 for the reasons set forth above, it follows that claims 6-8, 15, and 16 are not rendered obvious by Honeyman et al. in view of Laibinis et al.

Because claims 6-8, 15, and 16 are not rendered obvious by the hypothetical combination of Honeyman et al. in view of Laibinis et al., applicants request withdrawal of this rejection.

**REJECTION UNDER 35 U.S.C. § 103(a) – Honeyman et al. and Switzer et al.**

Claims 10 and 11 stand rejected under 35 U.S.C. § 103(a) as obvious over Honeyman et al. in view of Switzer et al. This rejection is traversed.

The Examiner cites Switzer et al. for the non-natural nucleotide spacers of claims 10 and 11. Claims 10 and 11 depend from claim 1. Because Honeyman et al. do not teach or suggest claim 1 for the reasons set forth above, it follows that claims 10 and 11 are not rendered obvious by Honeyman et al. in view of Switzer et al.

Because claims 10 and 11 are not rendered obvious by the hypothetical combination of Honeyman et al. in view of Switzer et al., applicants request withdrawal of this rejection.

**REJECTION UNDER 35 U.S.C. § 103(a) – Honeyman et al. and the Stratagene Catalog**

Claims 27-31 stand rejected under 35 U.S.C. § 103(a) as obvious over Honeyman et al. in view of the Stratagene Catalog. This rejection is traversed.

The Examiner cites the Stratagene Catalog for the kit of claims 27-31. Claims 27-31 depend from claim 1. Because Honeyman et al. do not teach or suggest claim 1 for the reasons set forth above, it follows that claims 27-31 are not rendered obvious by Honeyman et al. in view of the Stratagene Catalog.

Because claims 27-31 are not rendered obvious by the hypothetical combination of Honeyman et al. in view of the Stratagene Catalog, applicants request withdrawal of this rejection.

**REJECTION UNDER 35 U.S.C. § 103(a) – Hogan et al.**

Claims 1 and 32 stand rejected under 35 U.S.C. § 103(a) as obvious over Hogan et al. This rejection is traversed.

The Court of Appeals for the Federal Circuit has explained that the rationale to support a conclusion that a claim would have been obvious is that “a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success.” USPTO Examination Guidelines, 72 Fed. Reg. 195 (2007) quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006).

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

As recited in claim 32, the present invention is directed to a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

At page 8 of the Office Action under reply, the Examiner states that Hogan et al. teach a combination of a primer sequence and a helper sequence in which the helper sequence blocks intramolecular secondary hairpin target formation to facilitate PCR of target regions. Applicants submit that the Examiner's interpretation of Hogan et al. is not correct for at least the following reasons.

Hogan et al., which is discussed in the Background of the instant application, teach that secondary and tertiary structures that are not lost under conditions normally used for nucleic acid hybridization (e.g., elevated temperature, salt, and accelerators) may be disrupted through the use of helper oligonucleotides that bind to a portion of RNA or DNA other than that being targeted by the probe. According to Hogan et al., the helper oligonucleotides *impose new secondary or tertiary structures on the targeted region of the single stranded nucleic acid thereby accelerating the hybridization process* (col. 4, ll. 18-43). At col. 6, ll. 24-28, Hogan et al. explain that the effect of helper oligonucleotides on the kinetics of hybridization is the result of *reordering of the secondary and tertiary structure of the single stranded targeted nucleic acid*. At col. 7, ll. 19-27, Hogan et al. teach that in some cases, the helper oligonucleotide may be selected to bind to a region in the target nucleic acid that is immediately adjacent to the probe binding sequence. In such a case, limited overlap between the region binding the probe and the region binding to the helper can be tolerated, but is usually not desirable. In other cases, the helper may exhibit the desired effect even though it binds to a region removed from the region binding the probe. At col. 7, ll. 50-65, Hogan et al. teach that the helper oligonucleotide is typically used in excess compared to the target and/or the probe. When the probe is used in excess compared to the target, the helper oligonucleotide is typically used in a molar concentration of at least 5 times to more than 100 times that of the probe. When the target is in excess compared to the probe, the helper oligonucleotide typically is used in a molar concentration of at least 10 times to more than 100 times that of the probe.

Example 1 of Hogan et al. describes the use of two helper oligonucleotides to assist in the hybridization of the 16S rRNA of *Salmonella*, which exhibits a closed intrastrand helical structure in the 430-500 region of the 16S ribosome (Figure 2). Helper A was designed to bind in about the 430-450 region and Helper B was designed to bind in the 480-510 region; both Helpers were used in a molar concentration of 100 times that of the probe. Example 2 of Hogan et al. describes the use of nine helper oligonucleotides to assist in the hybridization of 16S rRNA

of *Neisseria*, which exhibits a closed intrastrand helical structure in the 130-150, 460-480, and 980-1010 regions (Figure 3). Helper C was designed to bind to the rRNA in the region immediately adjacent to the probe at about 110, Helpers D and E were designed to bind in regions of the rRNA remote from that bound by the probe at about 190 and 250, respectively; Helper F was designed to bind to the 450 region; Helper G was designed to bind to the 510 region; Helper H was designed to bind to the 35 region; Helper I was designed to bind to the 960 region; Helper J was designed to bind to the 1020 region; and Helper K was designed to bind to the 1210 region. Example 3 describes the use of two helper oligonucleotides to assist in the hybridization of region 450 of the 16S ribosomal RNA Of *E. coli*. The assays were run with a molar ratio of helper to probe of 250:1.

As noted above, in the Office Action under reply, the Examiner states that Hogan et al. teach a combination of a primer sequence and a helper sequence in which the helper sequence blocks intramolecular secondary hairpin target formation to facilitate PCR of target regions. On this characterization of Hogan et al., applicants note that Hogan et al. never references a “primer” and only uses the term “probe.” Further, Hogan et al. do not teach or suggest the use of the probe described therein for PCR (presumably because PCR was in its infancy at the November 24, 1987, filing date of Hogan et al.). Lastly, as discussed above, the method of Hogan et al. enhances hybridization not by breaking residual secondary or tertiary structures that remain after normal hybridization conditions, but rather, Hogan et al. enhances hybridization by using the helper sequences to reorder the secondary or tertiary structures on the targeted region so that the rate of hybridization of the probe is enhanced (*see*, col. 4, ll. 29-43; col. 6, ll. 25-30).

At page 8 of the Office Action, the Examiner admits that Hogan et al. do not teach the “primer” and helper in a single sequence, but asserts that one of skill in the art would have been motivated to combine the “primer” and the helper of Hogan et al. into a single sequence because primer design is routine and obvious to the skilled artisan. The Examiner adds that there are two ways to combine the sequences of Hogan et al., with a linking sequence or directly as a single contiguous sequence and that skilled artisan would have been motivated to combine the two sequences because a single sequence results in a lower cost assay, which is less labor intensive and more practical.

Applicants disagree with the Examiner’s obviousness analysis. Based solely on a reading of Hogan et al., there is no teaching or suggestion therein that would lead one of ordinary skill in

the art to be motivated to prepare a single sequence from the probe and excess helpers disclosed therein. As discussed above, Hogan et al. teach the use of multiple helper sequences that are in at least 5x molar excess of the probe sequence when the probe is used in excess to the target and at least 10x molar excess of the probe when the target is in excess to the probe (col. 7, ll. 50-65). The Examiner's obviousness analysis does not address the fact that the Hogan et al. helper sequences are in molar excess and consequently, provides no evidence on how one of skill in the art would be able to combine the molar excess helper sequences into the single probe sequence of Hogan et al.

Notwithstanding the foregoing, even if the ordinary artisan were to attempt to prepare a single probe that incorporates the helper sequences in the 5x to 100x molar excess taught by Hogan et al., the resulting probe would be so large that the ordinary artisan would not have a reasonable expectation that the probe would be successful at hybridizing to the target. The large size of the resulting single-stranded probe would likely result in the probe folding in upon itself and the presence of the molar excess helpers in the single-stranded probe would likely result in the crowding of the probe sequence rendering it ineffective for hybridization. Such a probe would not fulfill the purpose of Hogan et al., which is the enhancement of nucleic acid hybridization through the reordering of the secondary and tertiary structures on the target sequence (not on the probe) thus enhancing the rate of binding of the probe to the target region.

If the Examiner's reasoning for the motivation comes from another source, then pursuant to MPEP §2144.03, applicants request that the Examiner provide the source to applicants. If the Examiner's reasoning for the motivation is based upon judicial notice of facts not in the record or of information that the Examiner considers to be common knowledge in the art, then pursuant to MPEP § 2144.03, applicants request that the Examiner provide documentary evidence to support the judicial notice or the information that the Examiner considers to be common knowledge in the art. If the Examiner's reasoning for the motivation stems from personal knowledge, then pursuant to MPEP § 2144.03 and 37 C.F.R. 1.104(d)(2), applicants request that the Examiner submit an Affidavit or Declaration that introduces the Examiner's personal knowledge into the record for this case, along with a detailed description of how the Examiner's personal knowledge combined with Hogan et al. would result in the claimed invention.

Because the teachings of Hogan et al. do not render the claimed primers and probes obvious for the reasons set forth above, applicants request withdrawal of this rejection.

## **CONCLUSION**

With this paper, all of the Examiner's rejections have been fully addressed and overcome. Because there will be no outstanding issues for this matter upon entry of this paper, applicants request withdrawal of all claim rejections and passage of this application to issue.

Respectfully submitted,

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